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## Association Between Medication Adherence and the Outcomes of Heart Failure

*Running Head:* Medication Adherence and Heart Failure Outcomes

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### Abstract

**Background:** Previous studies of heart failure patients have demonstrated an association between cardiovascular medication adherence and hospitalizations or a composite end point of

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hospitalization and death. Few studies have assessed the impact of treatment adherence within large general medical populations that distinguish the health outcomes of emergency department visits, hospitalization, and death.

**Objective:** To determine the association of incremental cardiovascular medication adherence on emergency department visits, hospitalization, and death in adult heart failure patients in Indiana.

**Design:** Retrospective cohort study conducted using electronic health record data from the statewide Indiana Network for Patient Care (INPC) between 2004 and 2009.

**Methods:** Patients were at least 18 years of age with a diagnosis of heart failure and prescribed at least one cardiovascular medication for heart failure. Adherence was measured as the proportion of days covered (PDC) using pharmacy transaction data. Clinical end points included emergency department visits, hospital admissions, length of hospital stay, and mortality.

Generalized linear models were used to determine the effect of a 10% increase in PDC on clinical end points adjusting for age, sex, race, Charlson comorbidity index, and medications.

**Results:** Electronic health records were available for 55,312 patients (mean age  $\pm$  standard deviation [SD]  $68 \pm 16$  years; 54% women; 65% white). Mean PDC for all heart failure medications was  $63\% \pm 23\%$ . For every 10% increase in PDC, emergency department visits decreased 11% (rate ratio [RR] 0.89; 95% confidence interval [CI] 0.89-0.89), hospital admissions decreased 6% (RR 0.94; 95% CI 0.94-0.94), total length of hospital stay decreased 1% (RR 0.99; 95% CI 0.99-1.00), and all-cause mortality decreased 9% (odds ratio 0.91; 95% CI 0.90-0.92).

**Conclusion:** Incremental medication adherence was associated with reductions in emergency department visits, hospital admissions, length of hospital stay, and all-cause mortality.

Chronic heart failure affects more than 6.5 million Americans and its prevalence may increase to more than 8 million Americans by 2030.<sup>1</sup> It is a global disease, contributing to one in eight deaths and is increasing in areas where the risk factors for heart failure are common, such as in aging, ischemic heart disease, and hypertension.<sup>1</sup> Patients diagnosed with heart failure are often prescribed multiple medications for which they have low treatment adherence resulting in poor health outcomes and costly care.<sup>2</sup> Indeed, more than 500,000 heart failure-related hospitalizations occur each year with direct health care costs projected to reach \$69.7 billion in the United States by 2030.<sup>1</sup> It is well documented that adherence to medication is a vital part of the self-care management of heart failure.<sup>3-7</sup>

Notwithstanding, many heart failure patients fail to take their medications as prescribed at the risk of adverse health outcomes,<sup>8</sup> including death.<sup>9</sup> Interventions aimed at improving adherence to heart failure medications, however, reduce hospital readmissions and mortality.<sup>10</sup>

Many previous observational studies analyzing adherence had too few patients to examine an incremental effect of adherence on death or they focused mainly on patient characteristics rather than on health outcomes.<sup>3-7,11</sup> We identified multiple studies associating patient adherence to frequency of and time to clinical events such as cardiovascular<sup>7</sup> or heart failure-related hospitalizations or a composite end point of these end points coupled with death.<sup>3,4,6,11</sup> Studies of composite end points including death and those end points looking exclusively at hospitalizations had statistically significant results. However, these studies did not find a significant effect on death as an independent end point yet there were non-significant trends of an increased death rate with poor adherence. Our previous randomized trial of a pharmacist intervention aimed at improving adherence in heart failure patients had a favorable impact on emergency department visits and hospitalizations but had too few

participants to assess the effects of adherence on mortality.<sup>12</sup> We wanted to know whether the impact of improvements in treatment adherence translated to the broad population of patients in our state of Indiana so we conducted an observational study to determine the association between treatment adherence on health outcomes including urgent care, hospitalization, and death using data from a statewide health information exchange.

## Methods

### Patients

We extracted data from a health information exchange containing 55,312 patients with heart failure between January 1, 2004 and December 31, 2009. We included patients who were at least 18 years old, had an ICD9 code for heart failure (ICD9 codes 428.\*), and were prescribed at least one outpatient cardiovascular medication with at least two prescription refills to treat heart failure during the study period. Heart failure medications considered included angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, calcium-channel blockers, digoxin, diuretics, and the aldosterone antagonists, spironolactone or eplerenone. Prescription records were obtained from Surescripts®, a pharmacy transaction processing network that connects greater than 90% of retail pharmacies in Indiana, during the study period.<sup>13</sup>

### Data Source

Patients' digital health records were extracted from the Indiana Network for Patient Care (INPC). Most of the data extracted were coded elements. However, we attempted to obtain selected data such as functional health status using text mining of clinician notes within the health records. This health information exchange captures and stores digital health data across the state of Indiana including laboratory results, inpatient and outpatient encounter data (including urgent and emergent care), coded

diagnoses and procedures, and digital prescription records among other information from the major health care systems in Indiana.<sup>14</sup> The presence or absence of relevant comorbidities were derived from extracted ICD9 codes and physicians' problem lists for the patient and were used to calculate the Charlson Comorbidity Index for each patient.<sup>15</sup> Generally, this interconnected health exchange is invaluable in reducing missing data from patients who receive their care from more than one health care system. However, we could only report on results that were accessible from these digital health records. For example, if a patient did not have a particular laboratory test, there would be no accessible result for that test to extract. Most of the data for the present study derived from Marion County and surrounding counties (greater Indianapolis). Death data are available from the Indiana State Department of Health and, at the time of the data extraction, were most accurate from 2004 to 2009. All data were de-identified prior to analysis. The Indiana University Purdue University of Indianapolis (IUPUI) Institutional Review Board granted approval for this study.

### Study Design

This retrospective cohort study examined pharmacy transaction data for patients with heart failure to determine the percentage of days covered (PDC) as an estimate of their medication adherence. We used the method described by Nau<sup>16</sup> with a time off-set as recommended by Bijlsma and colleagues.<sup>17</sup> As proposed by Nau, we defined the PDC measurement frame as the date of the first/index prescription and the last date of the prescription plus the days covered with the last prescription or the last encounter in any one of the health systems of the INPC, or death. We then calculated the number of days by drugs in a specific class or overall drug classes. We then divided the number of days of drug coverage by the PDC measurement frame. We calculated the incremental adherence (in 10% increments) and examined the association of 10% increments on hospital admissions, number of emergency department visits, length of hospital stay, and all-cause mortality.

## Statistical Methods

Descriptive statistics including means and standard deviations for continuous data and counts and percentages for categorical data were calculated on patient characteristics and PDC usage. T-tests and one-way analysis of variance models were used to compare the PDC usage across patient characteristics. A mixed effects model with a random subject effect was used to compare PDCs from various drug classes. A logistic regression model was used to determine the effect of a 10% PDC increase on mortality. Similarly, Poisson regression models were used on the remaining aforementioned outcomes. Models were adjusted for patient age, self-identified race, sex, number of cardiovascular medications, and Charlson comorbidity index. We specified a p value of less than 0.05 as statistically significant.

## Results

### Patient Characteristics

Participants included in the study were mostly older adults with an average (standard deviation [SD]) age of  $68 \pm 16$  years old, women (54%), and white (65%) (**Table 1**). Patients were followed for a mean of  $4.7 \pm 2.2$  years of observation and prescription history (the range was 0-41.4 years, median 4.7 years, and the interquartile range [IQR] was 2.8-6.6 years). The range of refills was 2 to 2582 with a mean of  $151.4 \pm 155.8$ . We found limited data within the digital clinical notes on patient functional health status as measured by clinicians using the New York Heart Association (NYHA) classification (only 2.1% of patients), which were Class I (22%), II (37%), III (31%), or IV (10%). Patients had a mean of  $3.8 \pm 8.9$  emergency department visits,  $7.8 \pm 14.1$  hospitalizations, and a mean cumulative number of hospital days of  $36.4 \pm 108.4$  days (approximately 4.7 days per visit). There were 8515 (15%) deaths in the study.

The mean PDC  $\pm$  SD for all medications was  $63 \pm 23\%$  and varied by self-identified race/ethnicity. The PDC was highest for non-Hispanic Whites (65%), followed by Other race (60%), non-Hispanic African

Americans (57%), and Hispanics (50%) ( $p < 0.0001$ ). The mean PDC  $\pm$  SD was similar for men and women at  $62.8 \pm 22.8\%$  and  $62.7 \pm 22.5\%$ , respectively ( $p = 0.4916$ ). Additionally, the PDC varied by type of cardiovascular medication taken as shown in **Table 2**. In particular, diuretics had lower PDCs than the ACE inhibitors, ARBs, and beta-blockers ( $p < 0.0001$ , controlling for multiple comparisons). The multivariable model of the predictors of mortality including incremental changes in PDC is shown in **Table 3**. Notably, each 10% increase in overall PDC reduced the risk of death by 9% (odds ratio [OR], 0.91; 95% confidence interval [CI], 0.90-0.92). Compared to males, females had a slightly increased risk of death (OR, 1.06; 95% CI, 1.00-1.11). While the difference in mortality between black and white patients was not statistically significant, patients within the Other category of race/ethnicity who self-identified as Hispanic, Asian, Native American, Multiracial, or American Indian/Alaskan had a decreased risk of death compared with whites (OR, 0.45; 95% CI, 0.34-0.60). Age and comorbid conditions significantly increased the risk of death, but the numbers of cardiovascular drugs reduced this risk (OR, 0.84; 95% CI, 0.83-0.86).

As shown in **Table 4**, we found that improvements in adherence by 10% increments significantly reduced emergency department visits by 11% (rate ratio [RR], 0.89; 95% CI, 0.89-0.89), hospital admissions by 6% (RR, 0.94; 95% CI, 0.94-0.94), and total length of stay by 2% (RR, 0.99; 95% CI, 0.99-1.00). All utilization outcomes were statistically significant ( $p < 0.0001$ ). Compared with males, females had a greater RR for emergency department visits but a lower rate of hospitalizations and length of stay. Black and Other race had greater RRs than whites for emergency department visits, hospitalizations, and corresponding length of stay. In contrast to the reduced odds of death with greater numbers of cardiovascular drugs, the rate of utilization outcomes was greater as the number of cardiovascular drugs increased.

## Discussion

Our results suggest that increasing adherence to heart failure medications measured as a 10% increment has a favorable effect on health outcomes including reducing mortality by 9% (OR, 0.91; 95% CI, 0.90-0.92). We were particularly interested in the effects of adherence on mortality because there were few studies available that investigated such effects in patients with heart failure from the clinical setting. The association of cardiovascular drug adherence on health utilization in the present study generally agree with our previous study of a pharmacy intervention to improve adherence but the intervention study had too few participants to assess an effect of adherence on mortality. Nonetheless, data from randomized controlled drug trials,<sup>18,19</sup> a systematic review of interventions to improve adherence in patients with heart failure,<sup>10</sup> and one international registry study<sup>20</sup> would suggest an effect of treatment adherence on mortality. In the clinical setting, two key aspects are important: 1) physician prescribing evidence-based medications, and 2) patients taking their medications as prescribed. For clinicians, the widely accepted notion that treating heart failure to a targeted dosing goal is an effective way of improving outcomes, including reducing mortality;<sup>21</sup> however, prescribers may not always follow recommended guidelines.<sup>22-24</sup> Notwithstanding, even when clinicians follow evidence-based guidelines, health outcomes will not improve for patients who do not adhere to the therapy they have been prescribed.

Adherence to medication is associated with improved health outcomes including mortality,<sup>3-7</sup> but our study is among the first to look at electronic medical record data from a health information exchange in a large, longitudinal cohort of heart failure patients from general medical settings (N=55,312). We observed effects on age, sex, race, and comorbidity that we controlled for in the assessment of effects on health outcomes. Female patients had a slightly greater risk of death than males, which may be related to a less attention to cardiovascular risk factors<sup>25</sup> and lower prescribing of effective medications in women than in men.<sup>26</sup> The effects of race on mortality and utilization outcomes



could be the result of variation in cardiovascular medication prescribing to racial and ethnic minorities and their adherence to treatments.<sup>8,27</sup>

Class of medication has been linked to adherence rates in previous studies, specifically diuretics showing lower and beta-blockers showing higher adherence rates.<sup>28</sup> In contrast, patients taking statins, anticoagulants, antiarrhythmics, or fixed-dose combination products tended to have better adherence rates.<sup>28</sup> Consistent with these studies, we found lower adherence to diuretics compared with the other heart failure medications including beta-blockers. Adverse events such as increased urinary frequency with subsequent limits on patient mobility are also a possible explanation for patients not adhering to diuretics. Overall, our study also suggests a beneficial effect of cardiovascular medications in patients with heart failure from general clinical settings.

There are limitations to our study that are pertinent to address. Because we used predominantly coded digital data from the health information exchange, we were unable to control for important lifestyle effects such as diet and exercise, which could have a great impact on outcomes. Indeed, medication adherence may also be associated with adherence to a healthy lifestyle that would also improve outcomes. In a randomized controlled study of candesartan, even patients who did not receive active therapy had improved health outcomes with higher adherence to placebo.<sup>18</sup> Thus, adherence to medication therapy may be indicative of general “adherent behavior” in which patients also adhere to lifestyle advice.<sup>3,18</sup> Adherence is also influenced by levels of social support, comorbid conditions such as depression and dementia, and patients’ perceptions of the importance of taking medication.<sup>5-7,29-31</sup> Cognitive impairment is also a determinant of adherence and poor outcomes;<sup>32</sup> however, we did not have access to data on patient cognitive status. Our results included data for the period of 2004 to 2009 because our death data were valid and reconciled for this period. As such, newer drugs that have been shown to improve heart failure outcomes, such as sacubitril/valsartan and ivabradine, were not part of our adherence analysis. These drugs are slowly becoming an integral part

of heart failure treatment and future studies should examine how adherence affects outcomes with these medications.<sup>33</sup> It is also important to note that the PDC as a measure of adherence does not confirm that patients actually took their medications. Instead, the PDC only affirms medications were obtained from the pharmacy, suggesting that they were taken as prescribed. Finally, while the health information exchange allowed us to limit data that would otherwise be missing for patients visiting more than a single health system, we had limited data on NYHA classification, which was poorly documented in patients' clinical notes. Nonetheless, the limited data on NYHA class would not affect our primary results involving incremental changes in medication adherence and important health outcomes in patients with heart failure.

We conclude that incrementally increasing medication adherence reduces the risk of negative outcomes including death, emergency department visits, hospitalization, and length of hospital stay in heart failure patients. Our findings stress the importance of clinicians' active attention to improving adherence and thinking of adherence as a necessary component of effective pharmacotherapy.

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**Table 1. Patient Characteristics**

Characteristic	No. of Patients with Available Baseline Data	Mean $\pm$ SD or Frequency (%)
Number of patients, N	55,312	–
Mean age, years $\pm$ SD	55,312	67.7 $\pm$ 16.1
Sex, n (%)	55,312	
Female		29,528 (54)
Male		25,784 (46)
Race, n (%)	46,644	
White		36,245 (65)
Black		9766 (18)
Other		375 (0.68)
Hispanic		259 (0.47)
NYHA classification, n (%)	1153	
I		253 (22)
II		429 (37)
III		355 (31)
IV		116 (10)
Comorbidities, n (%)	55,102	
Hypertension		43,156 (78)
Diabetes		23,054 (41)
Chronic kidney disease		11,661 (21)
Coronary artery disease		29,788 (54)
Myocardial infarction		10,994 (20)
Hyperlipidemia		28,712 (52)
Atrial fibrillation		13,978 (25)
Stroke		5000 (9)
Chronic obstructive pulmonary disease		17,803 (32)

Depression		8398 (15)
Laboratory tests, mean $\pm$ SD		
Mean ejection fraction	10,759	50.9 $\pm$ 14
Mean pro-BNP level	20,790	563.9 $\pm$ 851
Mean body weight	14,252	202.9 $\pm$ 64
Mean systolic blood pressure <sup>a</sup>	6979	133.3 $\pm$ 18
Mean diastolic blood pressure <sup>a</sup>	6978	74.7 $\pm$ 11
Mean hematocrit	34,778	36 $\pm$ 14
Mean serum creatinine level	35,281	1.4 $\pm$ 1.3

BNP = brain natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation.

<sup>a</sup>Blood pressure measurements were the mean of clinic measurements while patients were sitting.



**Table 2. Mean PDC by Drug Class**

<b>Drug Class</b>	<b>N (%)</b>	<b>Mean PDC, % <math>\pm</math> SD<sup>a</sup></b>
Overall	--	63 $\pm$ 23
ACE inhibitor	30,599 (55)	63 $\pm$ 30
Anticoagulant	14,035 (25)	59 $\pm$ 30
ARB	14,368 (26)	65 $\pm$ 29
Aspirin/Antiplatelet	14,587 (26)	60 $\pm$ 32
Beta-blocker	38,461 (70)	64 $\pm$ 28
Any calcium channel blocker	21,613 (39)	63 $\pm$ 30
Digoxin	7368 (13)	63 $\pm$ 31
Loop diuretic	31,308 (57)	56 $\pm$ 31
Potassium-sparing diuretic	3366 (6)	54 $\pm$ 33
Statin	34,273 (62)	66 $\pm$ 28
Thiazide diuretic	17,689 (32)	54 $\pm$ 32
Any diuretic	39,733 (72)	60 $\pm$ 29

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; PDC = proportion of days covered; SD = standard deviation.

<sup>a</sup>A model comparing all drug classes excluding the overall has a  $p < 0.0001$ .

**Table 3. Results from Logistic Regression Model of All-Cause Mortality in Heart Failure Patients**

Category	Odds Ratio	95% CI	P value
10% PDC increase	0.91	0.90-0.92	<.0001
Gender (female vs. male)	1.06	1.00-1.11	0.0367
Race – overall <sup>a</sup>	--	--	<.0001
Black vs. white	1.00	0.94-1.07	0.9918
Other <sup>a</sup> vs. white	0.45	0.34-0.60	<.0001
Age at index	1.00	0.99-1.00	<.0001
Number of cardiovascular drugs	0.84	0.83-0.86	<.0001
Charlson Comorbidity Index	1.25	1.23-1.26	<.0001

CI = confidence interval; PDC = proportion of days covered.

<sup>a</sup>Other race includes the following number of individuals who self-identified their race as Hispanic (259), Other (255), Asian (102), Native American (11), Multiracial (3), and American Indian/Alaskan (2).

**Table 4. Results from Poisson Regression Models of Health Care Utilization in Heart Failure Patients**

Category	Rate Ratio	95% CI	P value
<b>Emergency Department Visits</b>			
10% PDC increase	0.89	0.89-0.89	<.0001
Age at index	0.99	0.99-0.99	<.0001
Gender (female)	1.04	1.03-1.05	<.0001
Gender (male)	1.00	1.00-1.00	-
Race (Black)	1.28	1.27-1.29	<.0001
Race (Other <sup>a</sup> )	1.12	1.08-1.16	<.0001
Race (White)	1.00	1.00-1.00	-
Number of cardiovascular drugs	1.02	1.02-1.02	<.0001
Charlson Comorbidity Index	1.13	1.13-1.14	<.0001
<b>Hospital Admissions</b>			
10% PDC increase	0.94	0.94-0.94	<.0001
Age at index	1.00	1.00-1.00	0.0019
Gender (female)	0.97	0.97-0.98	<.0001
Gender (male)	1.00	1.00-1.00	-
Race (Black)	0.77	0.76-0.78	<.0001
Race (Other <sup>a</sup> )	0.93	0.91-0.96	<.0001
Race (White)	1.00	1.00-1.00	-
Number of cardiovascular drugs	1.01	1.01-1.01	<.0001
Charlson Comorbidity Index	1.20	1.20-1.20	<.0001
<b>Length of Hospital Stay, days</b>			
10% PDC increase	0.99	0.99-1.00	<.0001
Age at index	1.00	1.00-1.00	<.0001
Gender (female)	0.97	0.96-0.97	<.0001
Gender (male)	1.00	1.00-1.00	-

Category	Rate Ratio	95% CI	P value
Race (Black)	1.10	1.10-1.10	<.0001
Race (Other <sup>a</sup> )	1.05	1.03-1.06	<.0001
Race (White)	1.00	1.00-1.00	-
Number of cardiovascular drugs	1.02	1.02-1.02	<.0001
Charlson Comorbidity Index	1.15	1.15-1.15	<.0001

CI = confidence interval; PDC = proportion of days covered.

<sup>a</sup>Other race includes the following number of individuals who self-identified their race as Hispanic (259), Other (255), Asian (102), Native American (11), Multiracial (3), and American Indian/Alaskan (2).